Wednesday, March 6, 1991
4:00PM–5:00PM, Room 216, East Concourse
Functional Abnormalities in the Failing Heart

4:00

ALTERATIONS IN Na^+,K^+-ATPase FUNCTION AND GLYCOSIDE RECEPTOR DENSITY ACCOMPANY CHRONIC SUPRAVENTRICULAR TACHYCARDIA (SVT) INDUCED CARDIOMYOPATHY

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Na^+,K^+-ATPase (NKA) is a major determinant of excitation/contraction where inhibition of NKA with glycosides such as digitalis improve inotropic state. Optimal glycoside therapy depends upon an intact NKA system, however changes in NKA activity and glycoside receptor density with the development of cardiomyopathy are not defined. Accordingly, LV function and NKA activity, glycoside binding, and immunolocation were examined in 7 cardiomyopathic pigs produced by atrial pacing for 3 weeks (SVT;240bpm) and 7 controls. Fractional shortening(FS), diastolic dimension(EDD), pressure(EDP), and stress(EDσ) were computed by echo/catheterization.

(*p<0.05)	FS(%)	EDD(cm)	EDσ(g/cm²)	EDP(mmHg)
Control	31±3	3.5±0.2	17±3	6±2
SVT	15±3*	5.1±0.2*	120±6*	22±4*

NKA activity was assayed as potassium p-nitro-phenol-phosphatase (μg pNP/mg/hr). Maximum number of glycoside receptors (Bmax) and affinity (Kd) were determined from ^{3}H-ouabain binding assays.

	ACTIVITY	Bmax(pmol/mg)	Kd(nM)
Control	0.64±0.06	5.5±0.4	15.3±3.4
SVT	0.45±0.12*	1.9±0.4*	8.8±2.6*

Immunohistochemistry revealed a reduction in sarcolemmal NKA content in SVT sections. Thus a potential mechanism for reduced NKA activity and glycoside receptor density is decreased myocyte NKA concentration. Altered NKA glycoside receptor density and affinity may attenuate the effectiveness of cardiac glycoside therapy in SVT induced cardiomyopathy. These changes in NKA activity and glycoside responsiveness may have important implications in the treatment of dilated cardiomyopathies.

4:15

ELEVATED CALMODULIN LEVELS IN END-STAGE HEART DISEASE

James B. Atkinson, Vanderbilt University, Nashville, TN

Abnormal Ca^{++} homeostasis may underlie myocardial dysfunction in end-stage heart disease. Calmodulin (CAL) is a Ca^{++}-binding protein that plays a major role in cell regulation. To further understand the role of Ca^{++} in heart disease, we measured CAL and Ca^{++} in the left ventricle of hearts from normal donors (controls, 6) and transplant patients with idiopathic dilated cardiomyopathy (IDC, 6), ischemic heart disease (IHD, 6) and valve disease (4).

	Control	IDC	IHD	Valve
CAL[a]	94±60	496±232[c]	405±235[d]	351±153[d]
Ca^{++}[b]	4±1	10±3[c]	11±3[c]	9±4[c]

mean ± SD; a ng/mg protein; b umol/gm dry wt; c P<0.01; d P<0.05.

Increases in CAL and Ca^{++} support the concept that calcium regulatory function is lost in end-stage myocardial disease. Although these changes may be compensatory in response to increased calcium influx into the myocyte, loss of calmodulin-mediated cell regulation may promote progression of myocardial dysfunction and could account for secondary degenerative changes in the heart.

4:30

MYOCARDIAL BIOENERGETIC ABNORMALITIES IN THE RAPID VENTRICULAR PACING MODEL OF CONGESTIVE HEART FAILURE

Timothy D. Henry, Jianyi Zhang, Minoru Yoshiyama, Vinaya Chepuri, Kamil Ugurbil, Arthur HL From, Robert J. Bache, Department of Medicine, University of Minnesota, Minneapolis, Minnesota, USA

Altered myocardial bioenergetics may play a role in the pathogenesis of congestive heart failure. The rapid ventricular pacing canine model has been shown to have hemodynamic, neurohumoral and mechanical abnormalities similar to dilated cardiomyopathy in humans. To evaluate the bioenergetic characteristics of this model, 8 acute open chest dogs were studied using P31 NMR spectroscopy after pacing at 250 beats/min for 17 days. The hearts were dilated without hypertrophy. Creatine phosphate (CP), ATP, and inorganic phosphate (Pi) were assessed via 5 layer transmural spectra in diastole. Hearts were studied at postpacing baseline, and during increased workloads with acute pacing (240 beats/min; AP), dobutamine (30 μg/min; D) and D+AP. Baseline mean LVEDP was 20, increased to 34 during AP and decreased to 8 during D. Whole wall CP/ATP ratio at post-pacing baseline was decreased compared to 14 control dogs: 2.01±.08 vs. 2.29±.07 (p=<.03). In hearts with failure, endocardial CP/ATP ratio decreased with AP from 2.11±.14 to 1.84±.19. In addition, Pi was detected at baseline in some hearts and in all hearts with AP or D+AP. In contrast, acute pacing in normal hearts produced no change in CP/ATP ratio and Pi was not present. These results indicate that bioenergetic abnormalities accompany the marked hemodynamic abnormalities in this model of congestive heart failure. This is reflected by the decrease in the CP/ATP ratio which is further reduced during the stress of acute pacing and the presence of Pi.

4:45

MYOCARDIAL α-ADRENERGIC TONE IMPAIRS ISOVOLUMIC RELAXATION IN THE FAILING HUMAN LEFT VENTRICLE.

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Purpose: The effect of myocardial α-adrenergic receptor stimulation on ventricular diastolic performance in man is unknown. Most in vitro investigations suggest that α-adrenergic stimulation slows the rate of myocardial relaxation. This investigation examined the effect of acute stimulation and blockade of myocardial α-adrenergic receptors on the rate of isovolumic relaxation in the failing and non-failing human left ventricle.

Methods: In 5 pts with normal LV function (Nls) and 7 pts with NYHA III-IV CHF, phenylephrine (PHP, final concentration 10 uM) and phentolamine (PTA, 0.2 mg/min) were infused into the left main coronary artery and high fidelity hemodynamics were recorded.

Results: Neither PHP or PTA affected HR or mean BP in either group. PHP had no effect on Tau or LVEDP in either group, although it did cause a significant increase in +dP/dt (p<0.05). Effects of PTA on Tau (ms) and LVEDP (mmHg) were as follows (mean ± SEM; * = p< 0.05 vs control; ** = p<0.03 vs Nls):

	Control	PTA		Control	PTA
Nls			CHF		
Tau	43±5	42±4		59±4 **	49±4 *
LVEDP	11±2	9±2		28±3 **	24±4 *

Conclusions: PHP had no effect on LV diastolic performance, possibly due to the opposing effects of the α- and β- adrenergic actions of this agent. However, selective α-adrenergic receptor blockade with PTA accelerates LV isovolumic relaxation in the failing, but not the non-failing human LV, suggesting that heightened sympathetic tone present in CHF may significantly effect LV diastolic performance due to stimulation of myocardial α-adrenergic receptors.